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PATENT SPECIFICATION (11) 1 499 485

(21) Application No. 10200/76 (22) Filed 15 March 1976
(31) Convention Application No. GO 1303
(32) Filed 14 March 1975 in
(33) Hungary (HU)
(44) Complete Specification published 1 Feb. 1978
(51) INT CL² C07C 157/07; A61K 31/17
(52) Index at acceptance
C2C 1173 200 220 221 225 226 227 22Y 311 313 31Y 323 32Y 332 338 360 361 364 36Y 380 694 695 697 750 753 754 75X 76X 78Y 790 79Y SM

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(54) NOVEL THIOCARBAMIDE DERIVATIVES AND PROCESS FOR THEIR PREPARATION

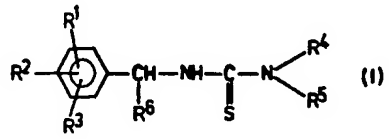
(71) We, EGYT GYOGYSZERVEGYESZETI GYAR, of 30, Kereszturi ut, Budapest X, Hungary, a Hungarian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel thiocarbamide derivatives.

Although several thiocarbamide derivatives are known, the following have not been reported to have favourable physiological properties. Such known compounds include 1-benzyl - 3 - (2 - hydroxyethyl) - thiocarbamide [Bull. Soc. Chim. France *5*, 960 (1960)]; 1 - (2 - chlorobenzyl) - 3 - (2-hydroxyethyl) - thiocarbamide, 1 - (4-chlorobenzyl) - 3 - (2 - hydroxyethyl)-thiocarbamide, 1 - (2 - methylbenzyl) - 3-(2 - hydroxyethyl) - thiocarbamide, 1 - (2,4-dimethylbenzyl) 3 - (2 - hydroxyethyl)-thiocarbamide, 1 - (2,5 - dimethylbenzyl)-3 - (2 - hydroxyethyl) - thiocarbamide [J. Indian Chem. Soc. *37*, 705 (1960)]; 1 - (4-bromobenzyl) - 3 - (2 - hydroxyethyl)-thiocarbamide [Helv. Chim. Acta *48*, 1069 (1965)]; 1 - (2 - methoxy - 4 - hydroxybenzyl) - 3 - (2 - hydroxyethyl) - thiocarbamide (Japanese Patent Application No. 7,017,524, December 24th, 1966); 1 - benzyl-3 - (3 - hydroxypropyl) - thiocarbamide [Acta Chem. Scand. *12*, 1746—58 (1958)]; 1 - benzyl - 3 - (4 - hydroxybutyl) - thiocarbamide, 1 - (4 - bromobenzyl) - 3 - (4-hydroxybutyl) - thiocarbamide [Helv. Chim. Acta *49*, 807 (1966)]; 1 - benzyl - 3 - (2-methylpropyl) - 3 - (2 - hydroxyethyl)-thiocarbamide, 1 - benzyl - 3 - bis - (2-hydroxyethyl) - thiocarbamide and 1 - benzyl-3 - (1,1 - dimethyl - 2 - hydroxyethyl)-thiocarbamide [Helv. Chim. Acta *48*, 1069 (1965)].

We have now discovered certain thiocarbamide derivatives that exhibit very favourable diuretic and saluretic effects, even when administered in small doses and others of low toxicity that reduce blood pressure or have analgesic or antidepressant effects.

Thus, the present invention consists in thiocarbamide derivatives having the general formula (I):



(I)

in which:

R^1, R^2 and R^3 are the same or different and each represents a hydrogen atom, a hydrocarbyl group which is unsubstituted or has one or more halogen substituents, a hydroxyhydrocarbyl group, a hydrocarbylaminohydrocarbyl group, a dihydrocarbylaminohydrocarbyl group, a hydrocarbyloxy group which is unsubstituted or has one or more halogen substituents, a hydroxy group, a dihydrocarbylamino group, an acylamino group, a nitro group, a sulphonic acid group or a halogen atom, said hydrocarbyl groups having from 1 to 8 carbon atoms and being straight or branched chain, saturated or unsaturated aliphatic hydrocarbyl groups;

R^4 represents a hydrogen atom or a saturated or unsaturated, straight or branched chain C_1 to C_8 aliphatic or alicyclic hydrocarbyl group, which is unsubstituted or has one or more hydroxy substituents;

R^5 represents a straight or branched chain aliphatic hydroxyhydrocarbyl group having from 2 to 6 carbon atoms or a straight or branched chain unsaturated aliphatic hydrocarbyl group having from 3 to 6 carbon atoms; and

R^6 represents a hydrogen atom, a hydrocarbyl group having from 1 to 7 carbon atoms which is unsubstituted or has one or more hydroxy, amino, hydrocarbylamino, dihydrocarbylamino or halogen substituents (said hydrocarbyl groups being straight or branched chain, saturated or unsaturated aliphatic hydrocarbyl groups or an alicyclic hydrocarbyl group having from 3 to 6 carbon atoms;

provided that R^6 does not represent a hydrogen atom when:

R^1, R^2, R^3 and R^4 each represents a hydrogen atom and R^5 represents a 2-hydroxyethyl, 3 - hydroxypropyl, 4 - hydroxybutyl or 1,1-dimethyl - 2 - hydroxyethyl group; or

R^2, R^3 and R^4 each represents a hydrogen atom, R^5 represents a 2-hydroxyethyl group and R^1 represents a 2-chloro, 4-chloro, 4-bromo or 2-methyl group; or

R^1 represents a 4-bromo group, R^2, R^3 and R^4 each represents a hydrogen atom, and R^5 represents a 4 - hydroxybutyl group; or

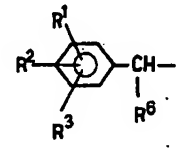
R^1 represents a 2-methyl group, R^2 represents a 4-methyl or 5-methyl group, R^3 and R^4 each represents a hydrogen atom, and R^5 represents a 2 - hydroxyethyl group; or

R^1 represents a 2-methoxy group, R^2 represents a 4-hydroxy group, R^3 and R^4 each represents a hydrogen atom, and R^5 represents a 2-hydroxyethyl group; or

R^1, R^2 and R^3 each represents a hydrogen atom, R^4 represents a 2-hydroxyethyl group or a 2-methylpropyl group, and R^5 represents a 2-hydroxyethyl group.

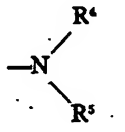
The compounds of formula (I) exist in the form of stereoisomers and the invention embraces the individual stereoisomers and mixtures thereof.

For example, the group:



may be:

benzyl, 2 - methylbenzyl, 3 - methylbenzyl, 4 - methylbenzyl, 2,3 - dimethylbenzyl, 2,4-dimethylbenzyl, 2,5 - dimethylbenzyl, 2,6-dimethylbenzyl, 2 - trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4 - trifluoromethylbenzyl, 4 - methoxybenzyl, 3,4 - dimethoxybenzyl, 2 - fluorobenzyl, 3 - fluorobenzyl, 4-fluorobenzyl, 2 - chlorobenzyl, 3 - chlorobenzyl, 4 - chlorobenzyl, 3,4 - dichlorobenzyl, 1 - phenylethyl, 1 - (4 - octylphenyl) - ethyl, 1 - (4 - methoxyphenyl) - ethyl, 1 - (2-fluorophenyl) - ethyl, 1 - (3 - fluorophenyl)-ethyl, 1 - (4 - fluorophenyl)ethyl, 1 - phenylpropyl, 1 - phenyl - 2 - methylpropyl, 1-phenylbutyl, 1 - phenyloctyl, phenyl - cyclopropylmethyl or phenyl - cyclohexylmethyl; and the group:



may be

2 - hydroxyethylamino, 2 - hydroxypropylamino, 3 - hydroxypropylamino, 2 - methyl-3 - hydroxypropylamino, 4 - hydroxybutylamino, allylamino, 2 - methylallylamino, N-methyl - N - (2 - hydroxyethyl) - amino, N - ethyl - N - (2 - hydroxyethyl) - amino, N - butyl - N - (2 - hydroxyethyl) - amino, N - cyclohexyl - N - (2 - hydroxyethyl)-amino or N - methyl - N - (3 - hydroxypropyl) - amino.

The present invention further consists in a pharmaceutical composition comprising a thiocarbamide derivative according to the invention in admixture with a pharmaceutically acceptable carrier and/or diluent and/or adjuvant.

Compounds of general formula (I) that produce a lasting blood pressure reduction include: 1 - (4 - chlorobenzyl) - 3 - (3-hydroxypropyl) - thiocarbamide, 1 - (4-fluorobenzyl) - 3 - methyl - 3 - (2 - hydroxyethyl) - thiocarbamide, 1 - (4 - chlorobenzyl) - 3 - methyl - 3 - (2 - hydroxyethyl)-thiocarbamide and 1 - (4 - trifluoromethylbenzyl) - 3 - methyl - 3 - (2 - hydroxyethyl) - thiocarbamide.

These compounds produced a blood pressure reduction of from 20 to 40% for more than 90 minutes when administered either intravenously or intraduodenally and in very low doses (e.g. from 0.1 to 1 mg/kg).

The diuretic and saluretic effects of certain of the compounds of general formula (I) are shown in Table II. The Lipschnitz method [J. Pharmacol. Ther. *79*, 97—110 (1943)] as modified by C. M. Kagawa and J. Kalm [Arch, Int. Pharmacodyn, *137*, 241—249 (1962)] was used.

The analgesic effect of certain of the compounds of general formula (I) is shown in Table III. The methods used were as follows:

Writhing test [L. B. Witkin et al. J. Pharm. exp. Ther. *133*, 400—408 (1961)] on mice;

Hot-plate test [J. Porszasz et al. Acta physiol. Acad. Sci. Hungary *4*, 107—113 (1953)] on mice; and

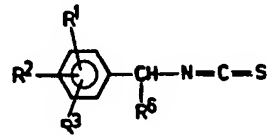
Randall-Sellito test [L. O. Randall and J. Sellito. Arch. Int. Pharmacodyn. *111*, 409—419 (1957)] on rats.

The antidepressant effect of certain of the compounds of general formula (I) is shown in Table IV. The method used was that of Berly M. Askew [Life Sci. *10*, 725 (1963)].

In addition to the uses mentioned above, compounds of general formula (I) can be used for the preparation of therapeutically valuable thiazaline, thiazolidine, thiazine, thiazepine and thiazocine derivatives.

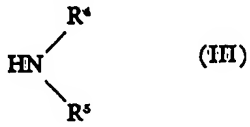
Compounds of general formula (I) can be prepared by any of the following methods; in the following description R^1 to R^6 have the same meanings as given above;

(a) by reacting an isothiocyanate of general formula (II):



(II)

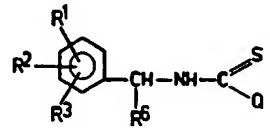
with an amine of general formula (III)



(III)

in a melt or in an inert solvent;

(b_1) by reacting a compound of general formula (IV):



(IV)

(in which Q represents an $-SR^7$ group, and R^7 represents a short-chain alkyl, an aryl or an aralkyl group) with an amine of general formula (III) in a melt or an inert solvent;

(b_2) by reacting a compound of general formula (IV) (in which Q represents a halogen atom) with an amine of general formula (III) in a melt or in an inert solvent; or

(b_3) by reacting a compound of general formula (IV) (in which Q represents an —SH group) with an amine of general formula (III) in the presence or absence of an inert solvent, and then melting the resulting salt. Chloroform, dichloroethane, tetrachloromethane and benzene are preferred solvents.

Certain of the isothiocayanatets of general formula (II) are known, others can be prepared by methods analogous to those used to prepare the known compounds [Org. Synth. Coll. Vol. 1, 2nd edition, page 447, John Wiley and Sons. Inc., New York, 1948); Chem. Ber. *101*, 1746 (1968)].

Secondary amines of general formula (III) are well-known and can be prepared by known methods [Houben-Weyl:Methoden der organischen Chemie, Vol. XI/1, pages 24, 267 and 1005, Georg Thieme Verlag, Stuttgart, (1957)].

Certain of the dithiocarbamic esters of general formula (IV) (Q represents $-SR^7$) are known, others can be prepared by methods analogous to those used to prepare the known compounds (Canadian Patent Specification No. 317,244; United States Patent Specifications Nos. 2,997,382 and 3,211,711 and Czechoslovak Patent Specification No. 133,718).

Certain of the thiocarbamic acid halides of general formula (IV) (Q represents halogen) are known, others can be prepared by methods analogous to those used to prepare the known compounds [Chem. Rev. *55*, 193 (1955)].

Dithiocarbamic acids of general formula (IV) (Q represents —SH) are readily formed from the corresponding amine and carbon disulphide in an inert solvent [Chem. Rev. *55*, 189 (1955)] and their salts formed with inorganic or organic bases can be easily identified.

The present invention is further illustrated by the following Examples:

EXAMPLE 1.
1-(4-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide

(a) A solution of 4 - fluorobenzyl isothiocyanate (12.6 g, 0.766 moles) in chloroform (100 ml) was added dropwise with stirring to an ice-cooled solution of ethanolamine (4.88 g, 0.08 mole) in chloroform (50 ml). The reaction mixture was refluxed for an hour, after which time the solvent was distilled off under vacuum, producing 17.45 g (100%) of yellow 1 - (4 - fluorobenzyl)-3 - (2 - hydroxyethyl) - thiocarbamide which had a honey-like consistency and which crystallized on standing. The product, after recrystallization from a 1:1 mixture of ethyl acetate and cyclohexane, had a melting point of 58—60°C.

(b) A mixture of methyl - N - (4-fluorobenzyl) - dithiocarbamate (21.5 g, 0.1 moles) and ethanolamine (12.2 g, 0.2 moles) was melted for 3 hours at 80°C. During the reaction methyl mercaptan was liberated from the mixture. Excess ethanolamine was removed from the reaction mixture by distillation under vacuum. The product (22.8 g, 100%), which had a honey-like consistency, was recrystallized from a 1:1 mixture of ethyl acetate and cyclohexane. The product melted at 58—60°C and was identical to that obtained in Example 1(a).

(c) A solution of methyl - N - (4-fluorobenzyl) - dithiocarbamate (21.5 g, 0.1 moles) and ethanolamine (7.32 g, 0.12 moles) in isopropanol (40 ml) was boiled for 3 hours, during which time methyl mercaptan was liberated from the reaction mixture. Isopropanol together with the excess ethanolamine was removed from the reaction mixture by vacuum distillation. The product (22.8 g, 100%), which had a honey-like consistency, was recrystallized from a 1:1 mixture of ethyl acetate and cyclohexane. The product melted at 58—60°C and was identical to that obtained in Example 1(a).

(d) The procedure of Example 1(c) was repeated except that boiling was carried out in chloroform instead of an isopropanol. The product (22.8 g, 100%), which had a honey-like consistency was recrystallized from a 1:1 mixture of ethyl acetate and cyclohexane, producing a compound which melted at 58—60°C. The product was identical to that obtained in Example 1(a).

(e) The procedure of Example 1(c) was repeated except that boiling was carried out in dioxane instead of in isopropanol. The product (22.8 g, 100%), which had a honey-like consistency was recrystallized from a 1:1 mixture of ethylacetate and cyclohexane, producing a compound which melted at 58—60°C. The product was identical to that obtained in Example 1(a).

(f) Carbon disulphide (3.02 ml, 0.05 moles) was added dropwise at 0°C with stirring to a solution of 4 - fluorobenzylamine (3.13 g, 0.025 moles) in anhydrous ethanol (25 ml) cooled with salted ice. The reaction mixture was stirred for half an hour at a temperature below 0°C, then, at the same temperature, ethanolamine (2.39 ml, 0.025 moles) was added dropwise and the mixture was stirred for a further half an hour at 0°C. The ethanol together with excess carbon disulphide was removed from the reaction mixture by distillation. The residual salt, which had a honey-like consistency, was heated for 1 hour on an oil bath at a temperature of 140°C, during which time hydrogen sulphide was liberated from the reaction mixture. After cooling, the product was dissolved in benzene (50 ml), shaken with water (3 lots of 50 ml each), dried and evaporated to dryness under vacuum. 1 - (4 - fluorobenzyl) - 3 - (2-hydroxyethyl) - thiocarbamide (4.85 g, 85%) having a honey-like consistency was produced. Recrystallization of the product from a 1:1 mixture of ethyl acetate and cyclohexane produced a product which melted at 57—60°C. The product was identical to that obtained in Example 1(a).

EXAMPLE 2.
1-(1-Phenylbutyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide

(a) A solution of 1 - phenylbutyl - isothiocyanate (23.3 g, 0.15 moles) in dichloroethane (100 ml) was added dropwise with stirring to an ice-cooled solution of 2-methylaminoethanol (12.0 g, 0.16 moles) in dichloroethane (50 ml). The reaction mixture was refluxed for 1 hour and then the solvent was evaporated under vacuum. 1 - (1-phenylbutyl) - 3 - methyl - 3 - (2 - hydroxyethyl) - thiocarbamide (39.9 g, 100%) which had a honey-like consistency and which crystallized on standing was produced. Recrystallization from ethyl acetate produced a product which melted at 74—75°C.

(b) A solution of 1 - phenylbutylamine (14.9 g, 0.1 moles) and thiophosgene (17.2 g, 0.15 moles) in anhydrous 1,2 - dichloroethane (100 ml) was stirred for 4 hours at room temperature and then evaporated to dryness under vacuum. The resulting N - (1-phenylbutyl) - thiocarbamyl chloride was dissolved in anhydrous benzene (50 ml). The solution was filtered and the filtrate slowly added dropwise with stirring to a solution of 2 - methylaminoethanol (16.5 g, 0.22 moles) in benzene (100 ml). The reaction mixture was then refluxed for 4 hours, allowed to cool, and treated with water (100 ml). The phases were then separated. The benzene solution was shaken with water (2 lots of 100 ml each), dried and evaporated to dryness under vacuum. In this way, a crude product (25.5 g, 95.7%) which had a honey-like consistency and which crystallized on standing was obtained. When recrystallized from ethyl acetate the product melted at 74—75°C, and was identical to that obtained in Example 2(a).

The compounds of general formula (I) listed in Table I were prepared by the methods of Examples (I) and (II). The compounds of Table I having a honey-like consistency were characterized by their R_f value. The developer was a 6:1 mixture of benzene and pyridine and the plate was a 0.1 to 0.2 mm layer of silica gel (Merck).

TABLE I

Number of Example	Compound	M.p. °C	R_f
3	± 1-(1-Phenylethyl)-3-(2-hydroxyethyl)-thiocarbamide	94–96	
4	± 1-(1-Phenylpropyl)-3-(2-hydroxyethyl)-thiocarbamide	97–98	
5	± 1-(1-Phenyl-2-methylpropyl)-3-(2-hydroxyethyl)-thiocarbamide	73–75	
6	± 1-(1-Phenylbutyl)-3-(2-hydroxyethyl)-thiocarbamide	95–96	
7	± 1-(1-Phenyloctyl)-3-(2-hydroxyethyl)-thiocarbamide	82–85	
8	± 1-(1-Phenyl-1-cyclopropylmethyl)-3-(2-hydroxyethyl)-thiocarbamide	97–98.5	
9	± 1-(1-Phenyl-1-cyclohexylmethyl)-3-(2-hydroxyethyl)-thiocarbamide	honey-like consistency	0.45
10	1-(3,4-Dimethoxybenzyl)-3-(2-hydroxyethyl)-thiocarbamide	115–117	
11	± 1-[-(4-Methoxyphenyl)-ethyl]-3-(2-hydroxyethyl)-thiocarbamide	84–87	
12	1-(2,6-Dimethylbenzyl)-3-(2-hydroxyethyl)-thiocarbamide	162–164	
13	± 1-[1-(4-Octylphenyl)-ethyl]-3-(2-Hydroxyethyl)-thiocarbamide	41–43.5	
14	1-(2-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide	109–110	
15	1-(3-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide	92–94	
16	1-(4-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide	59–61	
17	1-(3,4-Dichlorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide	91.5–92.5	
18	1-(2-Trifluoromethylbenzyl)-3-(2-hydroxyethyl)-thiocarbamide	88–90	
19	1-(3-Trifluoromethylbenzyl)-3-(2-hydroxyethyl)-thiocarbamide	48–50	
20	1-(4-Trifluoromethylbenzyl)-3-(2-hydroxyethyl)-thiocarbamide	80–84	
21	± 1-(1-Phenylethyl)-3-(3-hydroxypropyl)-thiocarbamide	129–131	
22	± 1-[1-(2-Fluorophenyl)-ethyl]-3-(2-hydroxyethyl)-thiocarbamide	103–105.5	

TABLE I (continued)

Number of Example	Compound	M.p. °C.	R_f
23	± 1-[1-(3-Fluorophenyl)-ethyl]-3-(2-hydroxyethyl)-thiocarbamide	honey-like consistency	0.25
23a	± 1-[1-(4-Fluorophenyl)-ethyl]-3-(2-hydroxyethyl)-thiocarbamide	91.5–92	
24	± 1-(1-Phenyl-2,2,2-trifluoroethyl)-3-(2-hydroxyethyl)-thiocarbamide	115–116.5	
25	± 1-(1-Phenylpropyl)-3-(3-hydroxypropyl)-thiocarbamide	120.5–122	
26	± 1-(1-Phenyl-2-methylpropyl)-3-(3-hydroxypropyl)-thiocarbamide	108–110	
27	1-(3,4-Dimethoxybenzyl)-3-(3-hydroxypropyl)-thiocarbamide	70–73	
28	± 1-[1-(4-Methoxyphenyl)-ethyl]-3-(2-hydroxyethyl)-thiocarbamide	117–118	
29	1-(2-Fluorobenzyl)-3-(3-hydroxypropyl)-thiocarbamide	100–102	
30	1-(3-Fluorobenzyl)-3-(3-hydroxypropyl)-thiocarbamide	99–100.5	
31	1-(4-Fluorobenzyl)-3-(3-hydroxypropyl)-thiocarbamide	117–119	
32	1-(4-Chlorobenzyl)-3-(3-hydroxypropyl)-thiocarbamide	124–125.5	
33	1-(3,4-Dichlorobenzyl)-3-(3-hydroxypropyl)-thiocarbamide	128.5–130.5	
34	1-Benzyl-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	54–56	
35	± 1-(1-Phenylethyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	honey-like consistency	0.51
36	± 1-(1-Phenylpropyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	80–82	
37	± 1-(1-Phenyl-2-methylpropyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	71–76	
38	± 1-(1-Phenylbutyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	74–75	
39	± 1-(1-Phenyloctyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	72–73.5	
40	± 1-(1-Phenyl-1-cyclopropylmethyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	114–116	
41	1-(3,4-Dimethoxybenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	89–91	

TABLE I (continued)

Number of Example	Compound	M.p. °C.	R_f
42	± 1-[1-(4-Methoxyphenyl)-ethyl]-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	62–65	
43	1-(2-Methylbenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	74–76	
44	1-(2,6-Dimethylbenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	120–121.5	
45	± 1-[1-(4-Octylphenyl)-ethyl]-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	52–55	
46	1-(2-Fluorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	63–65	
47	1-(3-Fluorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	61–63	
48	1-(4-Fluorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	103–105	
49	1-(2-Chlorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	honey-like consistency	0.40
50	1-(4-Chlorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	147–148	
51	1-(3,4-Dichlorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	104–106	
52	1-(2-Trifluoromethylbenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	93–94.5	
53	1-(3-Trifluoromethylbenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	78–80	
54	1-(4-Dimethylaminobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	108–110	
55	1-(4-Nitrobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	135–136.5	
56	1-(4-Fluorophenylethyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	honey-like consistency	0.88
57	± 1-(1-Phenyl-2,2,2-trifluoroethyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	107–110	
58	1-(4-Trifluoromethylbenzyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	91–92	
59	± 1-(1-Phenyl-2-methylpropyl)-3-ethyl-3-(2-hydroxyethyl)-thiocarbamide	82–84	
60	± 1-(1-Phenyl-2-methylpropyl)-3-butyl-3-(2-hydroxyethyl)-thiocarbamide	honey-like consistency	0.71

TABLE I (continued)

Number of Example	Compound	M.p. °C.	R_f
61	± 1-(1-Phenylethyl)-3-cyclohexyl-3-(2-hydroxyethyl)-thiocarbamide	89–90.5	
62	± 1-(1-Phenylethyl)-3,3-bis-(2-hydroxyethyl)-thiocarbamide	67–69	
63	± 1-(1-Phenylethyl)-3-allyl-thiocarbamide	56–59	
64	± 1-(1-Phenylpropyl)-3-allyl-thiocarbamide	honey-like consistency	0.75
65	1-(2-Fluorobenzyl)-3-allyl-thiocarbamide	50–53	
66	1-(4-Fluorobenzyl)-3-allyl-thiocarbamide	honey-like consistency	0.68
67	1-(3,4-Dimethoxybenzyl)-3-allyl-thiocarbamide	117–119	
68	± 1-(1-Phenylpropyl)-3-(2-methyl-allyl)-thiocarbamide	68–69	

TABLE II

Diuretic and saluretic effect of some compounds of the general formula I on rats

Compound	Oral dose mg./kg	Amount of urine		Electrolyte content of urine millimole/Kg/5 hrs.				
		ml./kg/5 hrs	T–C	Na^+	K^+	Cl^-	Na^+/K^+	$Cl^-/(Na^+ + K^+)$
1-(1-Phenylethyl)-3-(2-hydroxyethyl)-thiocarbamide	6	23.80	15.55	3.52	2.38	4.28	1.48	0.72
	54	35.40		4.92	2.23	5.13	2.21	0.72
1-(1-Phenylpropyl)-3-(2-hydroxyethyl)-thiocarbamide	6	24.00	17.70	3.98	1.03	4.37	3.85	0.89
	54	37.00	30.70	5.03	1.59	4.85	3.15	0.73
1-(2-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide	6	35.00	29.79	3.08	0.52	3.74	5.92	1.04
	54	37.00	31.39	3.55	0.66	4.29	5,88	1.02
1-(3-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide	6	27.20	19.30	3.70	0.96	4.20	3.95	0.90
	54	36.80	28.90	5.00	1.16	5.00	4.30	0.80
1-(2-Trifluoromethyl-benzyl)-3-(2-hydroxy-ethyl)-thiocarbamide	6	22.97	17.97	3.26	1.15	3.49	2.85	0.79
Average for the Control groups	–	5.65	5.65	0.78	0.49	1.01	1.59	0.80
Hydrochlorothiazide	6	19.45	13.80	3.11	1.16	4.09	2.72	1.03

Legend: T = test substance
C = control group
T–C = difference (in ml) between the amount of urine excreted by rats of the test group and the amount of urine excreted by rats of a control group on the same day.

Hydrochlorothiazide = 6-Chloro-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

TABLE III

Analgesic effect of some compounds of general formula I, on mice and rats

Compound	Writhing test ED_{50} mg/kg	Hot plate test ED_{50} mg/kg	Randall-Sellito test stimulation threshold
± 1-(Phenylethyl)-3-(2-hydroxyethyl)-thiocarbamide	3–10, oral	10–30 oral	200 mg/kg oral: 198% 100 mg/kg oral: 78% 50 mg/kg oral: 56%
± 1-(Phenylpropyl)-3-(2-hydroxyethyl)-thiocarbamide	3–10, oral	10–30, oral	200 mg/kg oral: 593% 100 mg/kg oral: 199% 50 mg/kg oral: 103%
± 1-Phenyl, cyclopropyl)-methyl-3-(2-hydroxy-ethyl)-thiocarbamide	10–30, i.p.	–	–
± 1-(1-Phenylethyl)-3-methyl-3-(2-hydroxy-ethyl)-thiocarbamide	10–30, oral	10–30, oral	200 mg/kg oral: 88% 100 mg/kg oral: 24% 50 mg/kg oral: 5%
Morphine	1.65 s.c.	2.50 s.c.	10 mg/kg s.c.: 1000% 3 mg/kg s.c. 90% 1 mg/kg s.c.: 9%
Propoxyphene (-(+)-1,2-diphenyl-3-methyl-2-propionyloxy-4-dimethylaminobutane)	22.5 oral	70, oral	100 mg/kg oral: 1000% 30 mg/kg oral: 534% 10 mg/kg oral: 33%
Amidazophene (1-Phenyl-2,3-dimethyl-5-pyrazolone	180 oral	60, oral	200 mg/kg oral: 100% 100 mg/kg oral: 69% 50 mg/kg oral: 8%

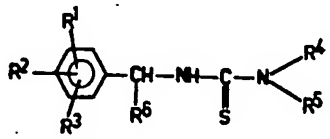
TABLE IV

Antidepressant effect of some compounds of general formula I on mice

Compound	Antagonization of the temperature-lowering action of reserpine	
	Dose mg/kg	Change in rectal temperature °C
± 1-(2-Fluorobenzyl)-3-(2-hydroxyethyl)-thiocarbamide	30	+ 3.4
± 1-(1-Phenylethyl)-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	30	+ 3.5
± 1-(1-Phenylpropyl-3-methyl-3-(2-hydroxyethyl)-thiocarbamide	30	+ 3.8
± 1-(4-Fluorobenzyl)-3-allyl-thiocarbamide	30	+ 3.8

WHAT WE CLAIM IS:—

1. Thiocarbamide derivatives having the general formula (I):



(I)

in which:

R^1, R^2 and R^3 are the same or different and each represents a hydrogen atom, a hydrocarbyl group which is unsubstituted or has one or more halogen substituents, a hydroxyhydrocarbyl group, a hydrocarbylaminohydrocarbyl group, a dihydrocarbylaminohydrocarbyl group, a hydrocarbyloxy group which is unsubstituted or has one or more halogen substituents, a hydroxy group, a dihydrocarbylamino group, an acylamino group, a nitro group, a sulphonic acid group or a halogen atom, said hydrocarbyl groups having from 1 to 8 carbon atoms and being straight or branched chain, saturated or unsaturated aliphatic hydrocarbyl groups:

R^4 represents a hydrogen atom or a saturated or unsaturated straight or branched chain C_1 to C_6 aliphatic or alicyclic hydrocarbyl group, which is unsubstituted or has one or more hydroxy substituents;

R^5 represents a straight or branched chain aliphatic hydroxyhydrocarbyl group having from 2 to 6 carbon atoms or a straight or branched chain unsaturated aliphatic hydrocarbyl group having from 3 to 6 carbon atoms; and

R^6 represents a hydrogen atom, a hydrocarbyl group having from 1 to 7 carbon atoms which is unsubstituted or has one or more hydroxy, amino, hydrocarbylamino, dihydrocarbylamino or halogen substituents (said hydrocarbyl groups being straight or branched chain, saturated or unsaturated aliphatic hydrocarbyl groups or an alicyclic hydrocarbyl group having from 3 to 6 carbon atoms;

provided that R^6 does not represent a hydrogen atom when:

R^1, R^2, R^3 and R^4 each represents a hydrogen atom and R^5 represents a 2-hydroxyethyl, 3 - hydroxypropyl, 4-hydroxybutyl or 1,1 - dimethyl - 2 -hydroxyethyl group; or

R^2, R^3 and R^4 each represents a hydrogen atom, R^5 represents a 2 - hydroxyethyl group and R^1 represents a 2-chloro, 4-chloro, 4-bromo or 2-methyl group; or

R^1 represents a 4-bromo group, R^2, R^3 and R^4 each represents a hydrogen atom, and R^5 represents a 4 - hydroxybutyl group; or

R^1 represents a 2-methyl group, R^2 represents a 4-methyl or 5-methyl group, R^3 and R^4 each represents a hydrogen atom, and R^5 represents a 2-hydroxyethyl group; or

R^1 represents a 2-methoxy group, R^2 represents a 4-hydroxy group, R^3 and R^4 each represents a hydrogen atom, and R^5 represents a 2-hydroxyethyl group; or

R^1, R^2 and R^3 each represents a hydrogen atom, R^4 represents a 2-hydroxyethyl group or a 2-methylpropyl group, and R^5 represents a 2-hydroxyethyl group.

2. 1 - (4 - Chlorobenzyl) - 3 - (3-hydroxypropyl) - thiocarbamide.

3. 1 - (4 - Fluorobenzyl) - 3 - methyl - 3-(2 - hydroxyethyl) - thiocarbamide.

4. 1 - (4 - Chlorobenzyl) - 3 - methyl - 3-(2 - hydroxyethyl) - thiocarbamide.

5. 1 - (4 - Trifluoromethylbenzyl) - 3-methyl - 3 - (2 - hydroxyethyl) - thiocarbamide.

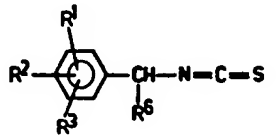
6. ± 1 - (1 - Phenylpropyl) - 3 - (2-hydroxyethyl) - thiocarbamide.

7. 1 - (2 - Fluorobenzyl) - 3 - (2-hydroxyethyl) - thiocarbamide.

8. ± 1 - (Phenylethyl) - 3 - (2-hydroxyethyl) - thiocarbamide.

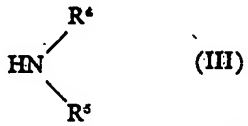
9. Thiocarbamide derivatives according to Claim 1, as herein specifically disclosed.

10. A process for preparing a thiocarbamide derivative according to Claim 1, in which an isothiocyanate having the general formula (II):



(II)

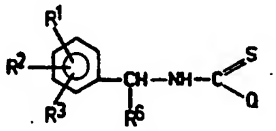
(in which R^1, R^2, R^3 and R^6 are as defined in Claim 1) is reacted with an amine of general formula (III):



(III)

(in which R^4 and R^5 are as defined in Claim 1) in a melt or in an inert solvent.

11. A process for preparing a thiocarbamide derivative according to Claim 1, in which a compound of general formula (IV):



(IV)

(in which R^1, R^2, R^3 and R^6 are as defined in Claim 1 and Q represents an —SR^7 group, wherein R^7 represents a short-chain alkyl group, an aryl group or an aralkyl group) is reacted with an amine of general formula

(III), as defined in Claim 10, in a melt or in an inert solvent.

12. A process for preparing a thiocarbamide derivative according to Claim 1, in which a compound of general formula (IV) (as shown in Claim 11 wherein R^1, R^2, R^3 and R^6 are as defined in Claim 1 and Q represents a halogen atom) is reacted with an amine of general formula (III), as defined in Claim 10, in a melt or in an inert solvent.

13. A process for preparing a thiocarbamide derivative according to Claim 1, in which a compound of general formula (IV) (as shown in Claim 11, wherein R^1, R^2, R^3 and R^6 are as defined in Claim 1 and Q represents an SH group) is reacted with an amine of general formula (III), as defined in Claim 10, to produce a salt, and the salt is then melted.

14. A process according to Claim 13, effected in the presence of an inert solvent.

15. A process according to any one of Claims 10 to 14, substantially as hereinbefore described with reference to any one of the foregoing Examples.

16. A thiocarbamide derivative when produced by a process according to any one of Claims 10 to 15.

17. A pharmaceutical composition comprising a thiocarbamide derivative according to any one of Claims 1 to 9 and 16 in admixture with a pharmaceutically acceptable carrier and/or diluent and/or adjuvant.

18. A pharmaceutical composition according to Claim 17, substantially as hereinbefore described.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.